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EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/780,035	Applicant(s) GHAYER ET AL.	
	Examiner Dong Jiang	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12 and 14-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *37 and 38* is/are allowed.

6)☒ Claim(s) *4-12,14-36,44-46 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4-12 and 14-61* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

The request filed on 29 June 2005 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/780,035 is acceptable, and a RCE has been established. An action on the RCE follows.

Applicant's amendment filed on 09 February 2005 is acknowledged and entered. Following the amendment, claims 4 and 44 are amended.

Currently, claims 4-12 and 14-61 are pending, and claims 4-12, 14-38, 44-46 and 61 are under consideration.

Withdrawal of Objections and Rejections:

The objection of claim 44 as being dependent upon a canceled claim is withdrawn in view of applicant's amendment.

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 29, 36 and their dependent claims 23-28, 32-35, and 44-46 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the last Office Action mailed on 09 August 2004, at pages 2-3.

Applicants argument filed on 09 February 2005 has been fully considered, but is not deemed persuasive for reasons below.

At page 12 of the response, the applicant argues that applicants disclose two variable regions in the specification, for example a VL and a VH, which can be joined to make a single protein chain (scFv), and that applicants disclose two anti-IL-18 single chain antibodies, both of

which are capable of binding IL-18 (Example 1), and therefore, applicants have sufficiently describbed an antibody or antigen-binding portion thereof comprising "at least two variable regions". This argument is not persuasive because the disclosed single chain antibodies comprise one variable region from L chain (VL), and one from H chain (VH). However, the claims, as written, encompass antibodies variable regions both from a L chain, or a H chain, which scope is different from that described in the specification, and therefore is not supported by the specification. The language such as "comprising one variable region from L chain, and one variable region from H chain" is suggested.

Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-36 and 44-46 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the previous Office Actions mailed on 20 November 2003 and 09 August 2004.

Applicants argument filed on 09 February 2005 has been fully considered, but is not deemed persuasive for reasons below.

At pages 13-14 of the response, the applicant argues that independent claims 22, 29 and 36 comprises "at least two variable regions", that as is well known in the art, and as defined in the specification, each variable region is comprised of three CDRs, that claims 25-36 further specify the amino acid sequences in the variable regions, and that one skilled in the art would recognize that applicants, at the time of filing, were in possession of the claimed invention and the specification as filed fully enable one skilled in the art. This argument is not persuasive because, as addressed in the previous Office Action, with exception of claims 37 and 38, the amino acid sequences recited in the claims (claims 30 and 31, for example) merely represent a small portion (11 or 17 amino acids in length), but not three CDRs of a light or a heavy chain.

As such, even though the claims *encompass* two variable regions or six CDRs by reciting "a light chain *variable region* and a heavy chain *variable region*", the sequence structure of at least two variable regions of one antibody chain is not defined. Therefore, a skilled artisan cannot envision the detailed chemical structure of the encompassed antibody or an antigen-binding portion thereof comprising SEQ ID NO:15 and 16 (or 17), and would not be able to make said antibody or an portion thereof capable of binding human IL-18.

Claims 22-36 and 44-46 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies and antigen-binding fragments thereof comprising one variable region from L chain, and one variable region from H chain, does not reasonably provide enablement for antibodies and antigen-binding fragments thereof variable regions both from a L chain, or a H chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argument filed on 09 February 2005 has been fully considered, but is not deemed persuasive for reasons below.

At page 14 of the response, the applicant further argues, besides those above, that applicants teach how to generate, screen and identify antibodies capable of binding IL-18, and one of ordinary skill in the art can readily comprehend the structural features necessary to generate antibodies to IL-18. This argument is not persuasive because, besides the reasons addressed above, it is not predictable that an antibody fragment comprising two variable regions of a L chain, or two variable regions of a H chain would have desired function. As such, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-12, 14-24, 44-46 and 61 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al. (US6,075,181, of record) and Dinarello et al. (J. Leukoc. Biol. 1998, 63:658-664. IDS #A4), for the reasons of record set forth in the previous Office Actions.

Applicants argument filed on 09 February 2005 has been fully considered, but is not deemed persuasive for reasons below.

At page 15 of the response, the applicant argues that Dinarello does not teach, suggest or motivate to generate fully human antibodies to IL-18, that Kucherlapati does not disclose IL-18, and does not teach, suggest or motivate to generate fully human antibodies to either IL-18, or specifically to human IL-18, that cited references, either singularly or in combination, do not teach, suggest or motivate the same, or method of making the same, and that the examiner fails to provide any evidence to support motivation to combine the cited art, and merely showing that all the elements of the claimed invention are known in the art is insufficient to establish obviousness. This argument is not persuasive for the following reasons. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the

teaching, suggestion, or motivation to make the claimed antibody can be readily found in the cited references as Dinarello teaches availability of human IL-18, the involvement of IL-18 in clinical pathology as that antibodies to IL-18 can inhibit the in vivo production of other pro-inflammatory cytokines, and that neutralizing anti-IL-l8 antibodies are a therapeutic option for specific blockade of IL-18. Additionally, Kucherlapati teaches a method of producing fully human monoclonal antibodies to *any protein* of interest, but *especially cytokines*, and advantages of such antibodies in avoiding the undesired immune responses elicited by administering non-human antibodies to humans. Therefore, it is instantly obvious to a person having ordinary skill in the art to combine the teachings of the cited references and to make the human anti-IL-18 antibodies as claimed for the purpose of disease treatment using the method taught by Kucherlapati.

At page 16 of the response, the applicant argues that without applicants disclosure, it is not obvious to make a leap from various therapeutic options as clinical strategy to block IL-18 to one specific cure, namely a human anti-IL-18 antibody, or to combine the teachings of the two references to arrive at applicants invention. This argument is not persuasive because none of the teachings, from which the instant rejection relies upon, is from applicants disclosure, instead they are all from the cited prior art references.

At page 17 of the response, the applicant argues, citing a case law (Cardiac Pacemakers Inc. v. St. Jude Medical, Inc. 381 F.3d 1371, 1377 (2004)), that recognition of a need does not render obvious the achievement that meets that need, and there is an important distinction between the general motivation to cure an uncured disease and the motivation to create a particular cure, that none of the cited art singularly or in combination, provides any teaching, suggestion, or motivation to arrive at applicants invention, and that a disclosure of a method to generate human monoclonal antibodies, combined with a reference disclosing neutralizing anti-IL-18 antibodies is not a clear and particular teaching, suggestion, or motivation to make the fully human anti-IL-18 antibody of the present invention. This argument is not persuasive for the following reasons. First, if either reference had explicitly taught the antibody as claimed, the present invention would have been rejected under 35 U.S.C. 102. Further, besides the reasons addressed above, the cited case law does not apply in the instant situation because in addition to the teachings of neutralizing anti-IL-18 antibodies, more importantly, Dinarello clearly teaches

1) the pathological role of IL-18 in disease development as that IL-18 is evolving as a major as a pro-inflammatory cytokine with implications for a role in inflammatory and infectious diseases, and it may also be a player in autoimmune diseases (page 658, the right column), and anti-IL-l8 antibodies suitable for treating human diseases, and 2) neutralizing anti-IL-l8 antibodies are a therapeutic option for specific blockade of IL-18. Furthermore, the prior art references teach disease treatment, and there is no such thing as the general motivation to cure an uncured disease in the references. Therefore, such argument is irrelevant. Furthermore, although Dinarello does not teach a human anti-IL-18 antibody or a method of making such, Kucherlapati teaches a method of producing fully human monoclonal antibodies to *any protein* of interest, but *especially cytokines*, and advantages of such antibodies. Therefore, the combined teachings provide strong teaching, suggestion, or motivation to arrive at applicants invention.

At pages 17-18 of the response, the applicant argues that the combination of the cited art is made by the examiner, upon guidance, direction, and motivation to do so, by applicants present invention, and that this is hindsight reconstruction and is impermissible as a basis for 103 rejection. This argument is not persuasive for the reasons addressed above. In addition, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion:

Claims 37 and 38 are allowable.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
8/2/05

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER